REMARKS

Applicant's attorney is appreciative of the interview granted by Examiners Richter and Sullivan on January 25, 2010. At that interview, Applicant's attorney presented arguments distinguishing the invention from the cited art, and the Examiners agreed that the claims were patentable over the cited art.

Claims 1, 2, 6 and 9-11 have been rejected under 35 USC 103(a) over Geczy in view of Grodzinska et al and Kinoshita et al.

The invention is directed to a method for attenuating development of atherosclerosis comprising administering molsidomine or one of its pharmaceutically acceptable salts daily, for a period of at least six months, in the form of a sustained-release solid oral composition containing between 14 and 24 mg of molsidomine effective over 24 hours.

As shown in the figure attached hereto and marked "Exhibit," atherosclerosis is thought to begin when the endothelial cells lining the vascular wall of arteries (step 1) are activated due to e.g. inflammation. This activation results in the (over)expression of cell adhesion molecules called ICAMs. These molecules are embedded into the endothelial cells membrane (i.e. they are insoluble and therefore non-circulating) so that it is practically impossible to test for their presence on the arterial lining directly.

These ICAMs can bind to circulating monocytes (step 3) and enable their migration into the vascular wall of the artery (step 4).

The subsequent reactions initiated by the integrated monocyte e.g. binding of low density lipoprotein (LDL) molecules (step 4) among others leads to the formation of foam cells which progressively reduce the diameter of the artery

lumen (step 5), therefore provoking the symptoms of atherosclerosis such as angina.

It was recently discovered that soluble versions of ICAMs (sICAMs), i.e. circulating in the plasma, could indicate the presence of insoluble ICAMs on the arterial lining and therefore be an indirect reading of the initiation or progression of atherosclerosis. Consequently, it is postulated that sICAMs are a specific biomarker of the atherosclerosis condition, meaning that increased plasma concentration of sICAMs is a sign of progression of atherosclerosis, whereas a diminution of the sICAM plasma concentration indicates that atherosclerosis is regressing.

As shown in the present application, long term administration of molsodomine according to the invention results in reduced concentration of sICAMs, and thus makes it possible to attenuate development of atherosclerosis.

The Geczy reference is clearly directed to treatment of angina with molsidomine. While angina is a symptom of atherosclerosis, nothing in Geczy suggests that long term treatment with molsidomine would attenuate development of atherosclerosis.

Grodzinska et al discusses treatment of patients with atherosclerosis of the lower limbs with molsidomine. The Grodzinska reference presents a study of 20 male patients suffering from atherosclerosis obliterans of the lower limbs being treated with molsidomine for up to 4 weeks with low doses thereof (page 40, column 1, end of third paragraph). In order to assess the effect of this treatment, the blood concentration of a number of biomarkers ECLT, t-PA, PAl and LDH from PMNs has been assayed (Abstract, second paragraph). It is crucial to note that none of these biomarkers has been shown to be specifically representative of the occurrence or the proliferation of atherosclerosis in humans.

It is clear from the detailed reading of the Grodzinska et al study that the contemplated use of molsidomine is to correct the EDRF (the natural NO producer deficiency) in patients with peripheral atherosclerosis (page 40, column 1, paragraph 2).

Grodzinska et al discusses improvements shown in patients treated by the short-course/low-dose molsidomine treatment as:

- "Molsidomine-treated patients showed some clinical improvement" (abstract, paragraph 3);

- "a beneficial effect of therapy with molsidomine was observed in 17 out of 20 patients" (page 40, column 2, first paragraph in the results section).

However, the results observed do not include an observed diminution or stabilization of the atherosclerosis condition, but, among others, to the increase distance of pain-free walking and the shortening of the period of pain relief after walking (page 40, column 2, first paragraph in the results section) or shortening of ECLT which are symptoms of the underlying condition i.e atherosclerosis.

The authors clearly acknowledge that "these effects of molsidomine may be attributed to its vasodilating action" (page 43, column 2, last sentence). The vasodilating action of molsidomine is known to treat the symptoms of atherosclerosis such as angina pectoris.

Thus, Grodzinska does not suggest that molsidomine can be used to treat the underlying disease, i.e. atherosclerosis.

The Kinoshita et al reference uses low doses of molsidomine (2 mg, page 1400, column 2, line 12) to "increase the exercise tolerance and the time up to the onset of ischaemia in patients with typical efforts angina" (page 1402, column 1, paragraph 4).

The Kinoshita reference is therefore not directed to the treatment of atherosclerosis but only discloses at most a

treatment to alleviate or ameliorate symptoms of this condition, i.e. angina.

Moreover, on page 1402, column 2, lines 6-8, it is clearly stated that "Our results indicate that long term treatment (using low doses of molsidomine) can induce a drug tolerance." The Kinoshita et al reference teaches that when a patient is treated with a low dose of molsidomine for up to 6 months, drug tolerance occurs, i.e. the reaction to the molsidomine treatment decreases, becoming less efficient or inefficient.

Thus, while molsidomine is known to alleviate symptoms of angina, Kinoshita et al clearly teaches one skilled in the art not to use a long treatment because tolerance will occur. Nothing in Kinoshita et al would suggest using molsidomine to attenuate development of atherosclerosis.

Accordingly, as agreed upon at the interview, the cited references teach only the treatment of symptoms of atherosclerosis after development of the disease. Since the claimed invention is directed to attenuation of development of atherosclerosis, which is not suggested by the cited references, withdrawal of this rejection is requested.

In view of the foregoing remarks, Applicant submit that the present application is now in condition for allowance. An early allowance of the application is earnestly solicited.

Respectfully submitted,

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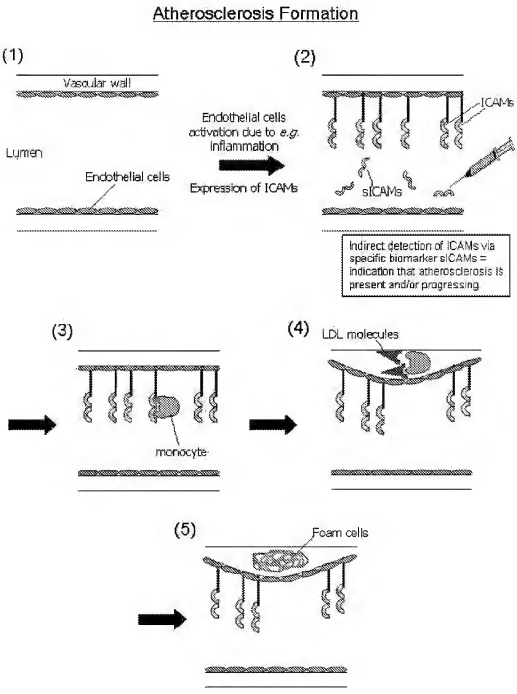
EXHIBIT


Atherosclerosis Formation
(1)
Vascular wall
Lumen
Endothelial cells
(2)
Endothelial cells activation due to e.g. inflammation
Expression of ICAMs
ICAMs
sICAMs
Indirect detection of ICAMs via specific biomarker sICAMs = indication that atherosclerosis is present and/or progressing
(3)
monocyte
(4)
LDL molecules
(5)
Foam cells